PATENT COOPERATION TREATY

Rec'd PCT/PTO 12 JAN 2005

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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MJW

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	23.03.2004
Applicant's or agent's file reference: X-15584	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 03/19554	11.07.2003	24.07.2002

Applicant
ELI LILLY AND COMPANY et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx. 523656 epmu d Fax: +49 89 2399 - 4465	Ullrich, J Tel. +49 89 2399-8048

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference X-15584	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US 03/19554	International filing date *(day/month/year)* 11.07.2003	Priority date *(day/month/year)* 24.07.2002
International Patent Classification (IPC) or both national classification and IPC C07D495/04, C07D495/04		
Applicant ELI LILLY AND COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04.11.2003	23.03.2004
Name and mailing address of the international preliminary examining authority. European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Weisbrod, T Telephone No. +49 89 2399-8931

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US 03/19554

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-40	as originally filed

Claims, Numbers

1-30, 31 (part)	as originally filed
31 (part), 32-36	filed with telefax on 23.09.2003

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 19-30

   because:

   ☒ the said international application, or the said claims Nos. 19-30 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-36
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-36
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-18,31-36
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item I

Basis of the opinion

With his FAX of 23.09.2003 the applicant filed replacement pages 46 and 47 to correct the numbering of the corresponding claims (cf. Rule 91.1 PCT).

The application is directed to
(i) compounds (I) (claims 1-17),
(ii) a pharmaceutical composition comprising compounds (I) (claim 18),
(iii) the corresponding therapeutic methods (claims 19-30),
(iv) intermediates (4) (claims 31-32),
(v) intermediates (10) (claims 33-34), and
(vi) intermediates (11) (claims 35-36).

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 19-30 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents.

D1: EP-A-0761669, 12.03.1997.
D2: Grese, T. A. *et al. J. Org. Chem.* **1998**, *41*(8), 1272-1283.

2 Novelty

D1 and **D2** relate to tetracyclic, conformationally restricted raloxifene analogues as selective estrogen receptor modulators. The present compounds (I) differ from the compounds of this prior art through the seven-membered ring within the tetracyclic ring system. Furthermore, intermediate compounds (4), (10), and (11) are not

disclosed in the said documents. The present claimed matter is, thus, novel in view of D1 and D2.

In view of the cited prior art the application complies with the criterion of novelty according to Article 33(2) PCT.

3 Inventive Step

3.1 The application describes the synthesis of certain compounds (I) via intermediates (4), (10), or (11), and shows that such compounds (I) represent estrogen receptor ligands (the application, pages 28-30; in particular, page 30, table).

3.2 In view of **D1** and/or **D2** as most relevant state of the art, the problem underlying the present application may be seen in the provision of further estrogen receptor ligands. The compounds of D1 and D2 represent, according to D2, conformationally restricted estrogen receptor modulators which incorporate structural elements of both raloxifene and of benzopyrane estrogen receptor modulators (cf. D2, page 1273, end of paragraph 1). However, none of the cited documents hints or suggests that the benzopyrane moiety of such hybrid estrogen receptor modulators might be replaced with the seven-membered ring moiety of the present compounds (I). Based on the unexpected retention of the desired activity, an inventive step may thus be acknowledged for compounds (I), subject matter referring to compounds (I), and intermediates (4), (10), and (11) for the preparation of such compounds (I). Consequently, the claims 1-36 appear to meet the requirements of Article 33(3) PCT.

4 Industrial Applicability

For the assessment of the present claims 19-30 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

5 Deficiencies of the Application under Article 6 PCT

Present claims 19-21 and 24-26 lack clarity because the vague phrases "a disease associated with estrogen deprivation" and "a disease associated with an aberrant physiological response to endogenous estrogen" leave the reader in doubt about the real diseases to which the claims refer. This objection may be overcome by replacing the objected phrases with specific real diseases in the light of the application as filed.

6 Further Deficiencies of the Application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D1 and D2 is not mentioned in the description, nor are these documents identified therein.

n is 2 or 3;

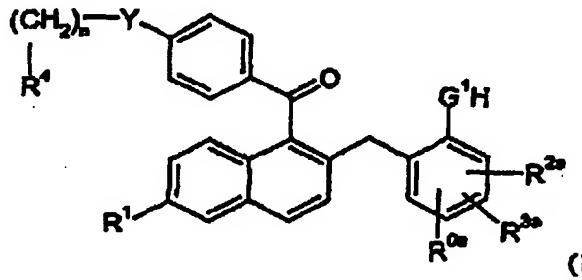
G^1 is –O–, –S–, or –N(R^5)–, wherein R^5 is –H or C_1-C_6 alkyl; and

Y is –O–, –S–, –NH–, –NMe–, or –CH_2–;

or a pharmaceutically acceptable salt thereof.

32. A compound according to Claim 31 wherein said compound is [6-hydroxy-2-(2-hydroxy-benzyl)-benzo[b]thiophen-3-yl]-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-methanone.

33. A compound of the formula



(10)

wherein

R^1 is -H, -OH, -O(C_1-C_4 alkyl), -$OCOC_6H_5$, -OCO(C_1-C_6 alkyl), or -OSO_2(C_2-C_6 alkyl);

R^{0a}, R^{2a} and R^{3a} are each independently -H, -OPg, or halo, wherein Pg is a hydroxy protecting group;

R^4 is 1-piperidinyl, 1-pyrrolidinyl, methyl-1-pyrrolidinyl, dimethyl-1-pyrrolidinyl, 4-morpholino, dimethylamino, diethylamino, diisopropylamino, or 1-hexamethyleneimino;

n is 2 or 3;

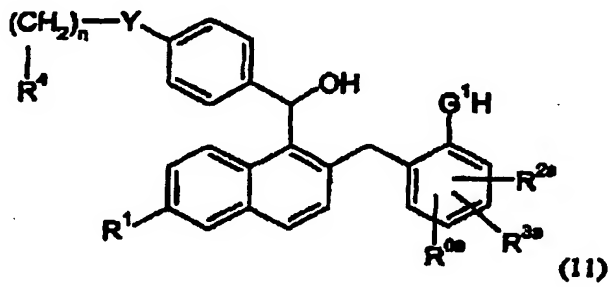
G^1 is –O–, –S–, or –N(R^5)–, wherein R^5 is –H or C_1-C_4 alkyl; and

Y is –O–, –S–, –NH–, –NMe–, or –CH_2–;

or a pharmaceutically acceptable salt thereof.

34. A compound according to Claim 33 wherein said compound is [6-hydroxy-2-(2-hydroxy-benzyl)-naphthalen-1-yl]-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-methanone.

35. A compound of the formula



(11)

wherein

R^1 is -H, -OH, -O(C_1-C_4 alkyl), -OCOC_6H_5, -OCO(C_1-C_6 alkyl), or -OSO_2(C_2-C_6 alkyl);

R^{0a}, R^{2a} and R^{3a} are each independently -H, -OPg, or halo, wherein Pg is a hydroxy protecting group;

R^4 is 1-piperidinyl, 1-pyrrolidinyl, methyl-1-pyrrolidinyl, dimethyl-1-pyrrolidinyl, 4-morpholino, dimethylamino, diethylamino, diisopropylamino, or 1-hexamethyleneimino;

n is 2 or 3;

G^1 is –O-, -S-, or –N(R^5)-, wherein R^5 is –H or C_1-C_4 alkyl; and

Y is –O-, -S-, -NH-, -NMe-, or -CH_2-;

or a pharmaceutically acceptable salt thereof.

36. A compound according to Claim 35 wherein said compound is 6-(2-hydroxy-benzyl)-5-(hydroxy-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-methyl)-naphthalen-2-ol.